AMENDMENTS TO THE CLAIMS:

This listing of claims will replace all prior versions, and listings, of claims in the application:

LISTING OF CLAIMS:

Claims 1-21 (Canceled as prosecuted in a previous application)

Claim 22. (Currently Amended): A method of inserting a heterologous gene coding sequence into an endogenous gene in a mouse embryonic stem cell genome and expressing said heterologous gene coding sequence, comprising the step of transforming the mouse embryonic stem cell with a random gene trap vector comprising a DNA construct, wherein the ~~DNA construct (k)~~ heterologous gene coding sequence lacks a promoter, and (ii) comprises the sequence:

~~5' A P B Q O 3'~~

~~in which~~

~~P is an internal ribosome entry site (IRES)~~

~~Q is the heterologous gene sequence, and~~

~~A, B and C are, separately, optional linker sequences;~~

~~wherein the DNA construct further comprises a polyadenylation signal at the 3' (downstream) end of Q and a splice acceptor site located 5' (upstream) of Q~~

5' X-A-P-B-Q-C-Y 3'

in which

~~comprises a splice acceptor sequence;~~

~~Y comprises a polyadenylation signal;~~

X and Y are separately, DNA sequences substantially homologous with a host gene locus;

P is an internal ribosome entry site (IRES);

Q is the heterologous gene sequence, including a translation start codon; and

A, B, and C are, separately, optional linker sequence[s];

wherein the DNA construct further comprises a polyadenylation signal at the 3' (downstream) end of Q and a splice acceptor site located 5' (upstream) of Q.

Claim 23. (Original): A method according to Claim 22 where the heterologous gene coding sequence is randomly inserted into an endogenous gene so that transcription of the heterologous gene coding sequence is directed by the host regulatory elements of the endogenous gene.

Claim 24. (Original): A method according to Claim 22 in which the splice acceptor permits functional integration of the heterologous gene coding sequence into an intron sequence.

Claim 25. (Canceled)

Claim 26. (Original): A method according to Claim 22 further comprising the step of identifying cells expressing the heterologous gene coding sequence.

Claim 27. (Currently Amended): A method according to Claim 26 wherein the ~~heterologous gene coding sequence~~ construct also ~~codes for~~ comprises a gene encoding a selectable marker and the method comprises selecting cells that express the selectable marker.

Claim 28. (Previously Amended) A mouse embryonic stem cell comprising a heterologous gene code sequence inserted by the method of Claim 22.

Claim 29. (Previously Amended) A descendant of the mouse embryonic stem cell according to Claim 28, wherein the descendant has inherited the inserted heterologous gene coding sequence.

Claim 30. (Withdrawn): An animal comprising a heterologous gene coding sequence inserted by the method of Claim 22.

Claim 31. (Withdrawn): A descendant of an animal according to Claim 30, wherein the descendant has inherited the inserted heterologous gene coding sequence.

Claim 32. (Currently Amended): A DNA construct for randomly inserting a heterologous gene sequence into a mouse cell genome, said ~~construct~~ heterologous gene sequence lacking a promoter and comprising the sequence:

~~5' — A-P-B-Q-C — 3'~~

~~in which~~

~~P is an internal ribosome entry site (IRES);~~

~~Q is a heterologous gene sequence; and~~

~~A, B and C are, separately, optional linker sequences;~~

~~wherein the DNA construct further comprises a polyadenylation signal at the 3' (downstream) end of Q and a splice acceptor site located 5' (upstream) of Q~~

5' X-A-P-B-Q-C-Y 3'

in which

	~~comprises a splice acceptor sequence;~~
~~Y~~	~~comprises a polyadenylation signal;~~
X and Y	are separately, DNA sequences substantially homologous with a host gene locus;
P	is an internal ribosome entry site (IRES);
Q	is the heterologous gene sequence, including a translation start codon; and
A, B and C	are, separately, optional linker sequence[s];

wherein the DNA construct further comprises a polyadenylation signal at the 3' (downstream) end of Q and a splice acceptor site located 5' (upstream) of Q.

Claim 33. (Original): A DNA construct according to Claim 32 in which the splice acceptor permits functional integration of the heterologous gene into an intron sequence.

Claim 34. (Currently Amended): A DNA construct according to Claim 32 in which the ~~heterologous gene sequence additionally codes for~~ construct also comprises a gene encoding a selectable marker to facilitate selection of mouse cells containing a heterologous gene that has been inserted into an endogenous gene.

Claim 35 (Withdrawn): A method of inserting a heterologous gene coding sequence into an endogenous gene in a eukaryotic cellular host cell genome and expressing said heterologous gene coding sequence, comprising the step of transforming the host cell with a random gene trap vector comprising a DNA construct, wherein the heterologous gene coding sequence (1) lacks a promoter, and (2) comprises the sequence:

5' X-A-P-B-Q-C-Y-Z 3'

in which

X	comprises a splice acceptor;
Y	comprises a polyadenylation signal;
P	is an internal ribosome entry site (IRES);
Q	is the heterologous gene sequence;
A, B, and C	are, separately, optional linker sequences; and
Z	is a selectable marker cassette optionally adapted for recombinatorial

deletion following introduction of an X-A-P-B-Q-C-Y-Z construct in a gene which is not expressed in ES cells.

Claim 36 (Withdrawn): A method according to Claim 35 wherein the heterologous gene coding sequence is inserted into an endogenous gene so that transcription of the heterologous gene coding sequence is directed by the host regulatory elements of the endogenous gene.

Claim 37 (Withdrawn): A method according to Claim 35 in which the splice acceptor permits functional integration of the heterologous gene coding sequence into an intron sequence.

Claim 38 (Withdrawn): A method according to Claim 35 wherein the heterologous gene coding sequence is expressed in an animal cell.

Claim 39 (Withdrawn): A method according to Claim 35 further comprising the step of identifying cells expressing the heterologous gene coding sequence.

Claim 40 (Withdrawn): A method according to Claim 36 wherein the heterologous gene coding sequence also codes for a selectable marker, such as antibiotic resistance, and the method comprises selecting cells that express the selectable marker.

Claim 41. (Currently Amended): A method according to Claim 22 wherein the ~~heterologous gene coding sequence~~ construct also ~~codes for~~ comprises a gene encoding antibiotic resistance, and the method comprises selecting cells that express the antibiotic resistance.

Claim 42. (Currently Amended): A DNA construct according to Claim 32 wherein the ~~heterologous gene sequence~~ construct additionally ~~codes for~~ comprises a gene encoding antibiotic resistance.

Claims 43-46 (Canceled)

Claim 47. (New): A method of inserting a heterologous gene coding sequence into an endogenous gene in a mouse embryonic stem cell genome and expressing said heterologous gene coding sequence, comprising the step of transforming the mouse embryonic stem cell with a random gene trap vector comprising a DNA construct, wherein the heterologous gene coding sequence lacks a promoter, and comprises the sequence:

5' A-P-B-Q-C 3'

in which

P	is an internal ribosome entry site (IRES);
Q	is the heterologous gene sequence, and
A, B and C	are, separately, optional linker sequences;

wherein the DNA construct further comprises a polyadenylation signal at the 3' (downstream) end of Q and a splice acceptor site located 5' (upstream) of Q.

Claim 48. (New): A method according to Claim 47 where the heterologous gene coding sequence is randomly inserted into an endogenous gene so that transcription of the

heterologous gene coding sequence is directed by the host regulatory elements of the endogenous gene.

Claim 49. (New): A method according to Claim 47 in which the splice acceptor permits functional integration of the heterologous gene coding sequence into an intron sequence.

Claim 50. (New): A method according to Claim 47 further comprising the step of identifying cells expressing the heterologous gene coding sequence.

Claim 51. (New): A method according to claim 50 wherein the construct also comprises a gene encoding a selectable marker and the method comprises selecting cells that express the selectable marker.

Claim 52. (New): A mouse embryonic stem cell comprising a heterologous gene coding sequence inserted by the method of Claim 47.

Claim 53. (New): A descendant of the mouse embryonic stem cell according to Claim 52, wherein the descendant has inherited the inserted heterologous gene coding sequence.

Claim 54. (New): A mouse comprising a cell according to Claim 53.

Claim 55. (New): A descendant of a mouse according to Claim 54, wherein the descendant has inherited the inserted heterologous gene coding sequence.

Claim 56. (New): A DNA construct comprising the sequence:

5' A-P-B-Q-C 3'

in which

P	is an internal ribosome entry site (IRES);
Q	is a heterologous gene sequence; and
A, B and C	are, separately, optional linker sequences;

wherein the DNA construct further comprises a polyadenylation signal at the 3' (downstream) end of Q and a splice acceptor site located 5' (upstream) of Q.

Claim 57. (New): A DNA construct according to Claim 56 in which the splice acceptor permits functional integration of the heterologous gene into an intron sequence.

Claim 58. (New): A DNA construct according to Claim 56 in which the construct also comprises a gene encoding a selectable marker to facilitate selection of cells containing a heterologous gene that has been inserted into an endogenous gene.

Claim 59. (New): A method according to Claim 47, wherein the construct also comprises a gene encoding antibiotic resistance, and the method comprises selecting cells that express the antibiotic resistance.

Claim 60. (New): A DNA construct according to Claim 56, wherein the construct additionally comprises a gene encoding antibiotic resistance.

Claim 61. (New): A mouse comprising a heterologous gene coding sequence inserted by the method of claim 22.

Claim 62. (New): A descendant of the mouse according to Claim 61, wherein the descendant has inherited the inserted heterologous gene coding sequence.

Claim 63. (New): A cell comprising a heterologous gene coding sequence inserted according to the method of Claim 56.

Claim 64. (New): A descendant of the cell according to Claim 63, wherein the descendant has inherited the inserted heterologous gene coding sequence.

Claim 65. (New): A mouse comprising a heterologous gene coding sequence inserted according to the method of Claim 56.

Claim 66. (New): A descendant of the mouse according to Claim 65, wherein the descendant has inherited the inserted heterologous gene coding sequence.

Claim 67. (New): A cell comprising an inserted heterologous gene coding sequence inserted into a target endogenous gene in a eukaryotic cellular host cell genome by transforming the host cell with a vector comprising a DNA construct, wherein the DNA construct comprises the elements:

5' X-A-P-B-Q-C-Y 3'

in which

X and Y	are substantially homologous with separate sequences from the target endogenous gene and are of sufficient length to undergo homologous recombination with the host cell genome so as to insert the A-P-B-Q-C elements into the host cell genome;
P	is an internal ribosome entry site (IRES);
Q	is the heterologous gene coding sequence; and
A, B, and C	are, separately, linker sequence or a covalent bond.

Claim 68. (New): A descendant of the cell of Claim 67, wherein the descendant has inherited the inserted heterologous gene coding sequence.

Claim 69. (New): A mouse comprising an inserted heterologous gene coding sequence inserted into a target endogenous gene in a eukaryotic cellular host cell genome by transforming the host cell with a vector comprising a DNA construct, wherein the DNA construct comprises the elements:

5' X-A-P-B-Q-C-Y 3'

in which

X and Y	are substantially homologouse with separate sequences from the target endogenous gene and are of sufficient length to undergo homologous recombination with the host cell genome so as to insert the A-P-B-Q-C elements in to the host cell genome;
P	is an internal ribosome entry site (IRES);
Q	is the heterologous gene coding sequence; and
A, B, and C	are, separately, linker sequence or a covalent bond.

Claim 70. (New): A descendant of the mouse of Claim 69, wherein the descendant has inherited the inserted heterologous gene coding sequence.

Claim 71. (New): A cell according to Claim 67, wherein the construct also comprises a gene encoding a selectable marker.

Claim 72. (New): A mouse according to Claim 69, wherein the construct also comprises a gene encoding a selectable marker.

Claim 73. (New): A DNA construct for inserting a heterologous gene coding sequence into a target endogenous gene in a eukaryotic cellular host cell genome, wherein the construct comprises the elements:

5' X-A-P-B-Q-C-Y 3'

in which

X and Y	are substantially homologous with separate sequences from the target endogenous gene and are of sufficient length to undergo homologous recombination with the host cell genome so as to insert the A-P-B-Q-C elements into the host cell genome;
P	is an internal ribosome entry site (IRES);
Q	is the heterologous gene coding sequence; and
A, B, and C	are, separately, linker sequence or a covalent bond.

Claim 74. (New): The DNA construct according to Claim 73, wherein the construct also comprises a gene encoding a selectable marker.

REMARKS

The Applicant acknowledges, with thanks, receipt of the Office Action mailed February 6, 2003.

Claims 22-24, 26-34 and 41-42 are pending, and new claims 47-74 have been added. The action by the Examiner of this application, together with the cited references, have been given careful consideration. It is respectfully requested that the Examiner reconsider the claims in their present form, together with the following comments, and allow the application.

The Examiner denied Applicant's claim of priority based on the rejections of claims 22-24, 26-29, 32-34 and 41-42 under 35 U.S.C. §112, First Paragraph. The Examiner rejected claims 22-24, 26-29, 32-34 and 41-42 under 35 U.S.C. §112, First Paragraph as it relates to New Matter. Specifically, it was the Examiner's position that the claims contain new subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventors had possession of the claimed invention. Further, the Examiner rejected claims 22-24, 26-29, 32-34 and 41-42 under 35 U.S.C. §112, First Paragraph as it relates to Enablement. Specifically, the Examiner stated the claims do not enable one skilled in the art to make and/or use the invention. The Examiner rejected claims 22-24, 26-29, 32-34 and 41-42 under 35 U.S.C. §102(e) as being anticipated by Tessier-Lavigne et al. (U.S. Patent No. 6,248,934). Applicant respectfully traverses the rejections.

Claims 22-24, 26-29, 32-34 and 41-42 are entitled to Priority

In light of the arguments on New Matter and Enablement set forth below, Applicant's claim of priority to 08/537,765 (U.S. Patent No. 6,150,169) should be reconsidered and these claims should be entitled to priority.

Claims 22-24, 26-29, 32-34 and 41-42 are in Condition for Allowance

Under 35 U.S.C. §112, 1st Paragraph; as it relates to New Matter

Claims 22-24, 26-29, 32-34 and 41-42 were rejected under 35 U.S.C. §112, 1st Paragraph. Specifically, the Examiner has raised an objection that Claims 22 and 32 contain new matter and, in particular, that there was no support for a construct lacking the X and Y homologous sequences. Applicant respectfully traverses. Claim 22 and 32 have been amended to restore the original definition of the construct as 5' X-A-P-BQ-C-Y 3' and to specify that X and Y are homologous sequences. The applicant retains the qualifications that the construct lacks a promoter and that it further comprises a polyadenylation signal downstream of the heterologous gene sequence and a splice acceptor site upstream of the heterologous sequence. Support for a promoterless construct can be found in the first complete paragraph of page 14, support for the polyadenylation signal can be found in the paragraph bridging pages 10 and 11 and in original claim 7, and support for the splice acceptor site can be found in original claim 8 and on page 11, lines 8-9.

New claims 47-60 contain support for gene trap constructs. It is known in the art that gene trap vectors lack promoters and generally lack homologous sequences. The following enclosed prior art documents, as included in the attached IDS, show that that is known in the art. These documents are discussed in more detail below.

Specifically, Friedrich *et al.* describes promoterless constructs for use in promoter trapping (abstract). Further support for promoterless constructs is found on page 1513, column 2, line 28 to page 1514, column 1, line 22, and page 1514, column 1, first paragraph following the heading "Results". The construct used is described in more detail on page 1521, columns 1-2 in the section headed "Construction of plasmids and retroviral vectors". It can be seen from this passage that the construct has a splice acceptor, a β-galactosidase fragment that lacks a promoter and a neo gene cassette. In addition, it is clear that this construct lacks homologous sequences.

Skarnes *et al.* describes gene traps. It is clear from page 904, column 1, lines 15-31 that gene trap constructs include a splice acceptor upstream of a promoterless gene. These constructs do not have homologous sequence elements.

Joyner provides a review of enhancer and gene trap screens and, separately, the use of homologous recombination for generating targeted mutations in Embryonic Stem cells (abstract). Page 651, column 1, lines 28-39 again indicates that gene trap vectors do not contain a promoter and have a splice acceptor upstream of the heterologous gene. It will also be seen that the constructs described lack homologous sequence elements.

Gossler *et al.* describes enhancer traps using a minimal promoter and gene traps using constructs lacking a promoter in Embryonic Stem cells (see Figure 1 and page 464, paragraph spanning columns 1 and 2). Again, the vectors described lack homologous sequences.

Robertson *et al.* describes the use of retroviral vectors to introduce DNA into embryonic stem cells using random integration (page 447, column 1, first full paragraph) and describes a construct which, in this case, has a promoter but lacks homologous sequences (see Figure 2).

Thus, the nature of gene trap vectors is well known in the prior art at the priority date, and as such, it would have been understood that such vectors lack promoters and need not comprise homologous sequences.

Additionally, the Examiner's objection that random integration can occur when homologous sequences X and Y are present, is correct. However, it is also clear from the documents discussed above, that homologous sequences need not be present in constructs used for random integration. Therefore, all claims are in condition for allowance under §112.

Claims 22-24, 26-29, 32-34 and 41-42 are in Condition for Allowance
<u>Under 35 U.S.C. §112, 1st Paragraph as it relates to Enablement</u>

The Examiner again objected that there is no teaching concerning the insertion of a construct 5'A-B-P-Q-C 3' (i.e. a construct lacking homologous sequences X and Y) into an

endogenous mouse gene or a mouse cell comprising such a sequence, and that a person of skill in the art would not know how to use the claimed invention, particularly as there is no example dealing particularly with the random integration embodiments. The following documents show that gene trap technology was well established at the priority date and that a skilled person would have known how to use it in the context of the present invention.

For example, Friedrich describes how to use a promoter trap and select cells in which promoter trap events have occurred by selecting for cells having acquired resistance to the antibiotic G418 through expression of the β-geo reporter under the control of an endogenous promoter (page 1513, column 2, line 28 - page 1514, column 1, line 22). Page 1514, column 1, the first paragraph of "Results" and page 1517, column 2, first paragraph of "Discussion" both indicate promoter trapping involves the introduction of a reporter gene lacking a promoter and homologous sequence elements into cells, here embryonic stem cells, and that expression of the reporter relies on insertion of the construct in the correct orientation under the control of an endogenous promoter.

Similarly, Skarnes describes how a gene trap construct can be used. For example, page 904, column 1, lines 15-31 indicates how promoterless constructs lacking homologous sequences can be used such that the reporter gene is expressed when the construct integrates in an appropriate position and orientation.

Joyner also describes how gene trap vectors can be used. These vectors, which lack a promoter, can be randomly integrated into the genome of a cell and the reporter gene, in this case Lac Z, can be activated and expressed if the construct integrates in the correct orientation and reading frame to be compatible with endogenous gene sequences (page 651, column 1, lines 28-39).

The Examiner further objected that the use of random integration would cause unpredictability and require undue experimentation to use the claimed invention, particularly in the context of generating transgenic mice.

However, the present invention is directed to the random integration of a construct into the genome of a mouse embryonic stem cell. The construct claimed is a promoterless gene trap construct and expression of the heterologous gene which only occurs when the construct integrates in the correct position and orientation such that it is under the control of an endogenous promoter. It would have been well known at the priority date that such rare integration events could be identified through the use of gene trap technology in Embryonic Stem cells.

For example, Joyner indicates that the separate techniques of gene traps and targeted mutation using homologous recombination are both rare genetic events that can be easily screened in mouse embryonic stem cells (abstract, page 650, column 2, lines 25-30). This is confirmed in Gossler which teaches that the use of gene trap vectors in embryonic stem cells permits selection for rare-occurring integration events (page 463, column 3, final paragraph). This is contrasted to the technique of micro-injecting fertilised eggs, which is the technique described in the references by Wall and Houdebine referred to by the Examiner. Both Joyner and Gossler show how transgenic mice can readily be generated from Embryonic Stem cells in which a desired integration event has occurred (see Joyner Figures 1 and 2, and Gossler page 244, column 3, first and second full paragraphs).

The Examiner's argument concerning unpredictability of random integration relies heavily on the citations by Wall and Houdebine enclosed with the previous Office Action. As mentioned above, these documents are not concerned with the use of gene trap vectors in embryonic cells and subsequence creation of transgenic animals. Rather these documents relate to the creation of transgenic animals through pronuclear micro-injection of pre-implantation embryos.

Specifically, Wall is concerned with the generation of transgenic livestock, especially the introduction of transgenes by pronuclear micro-injection (see abstract and page 57, first paragraph of Introduction). This process is completely different to the creation of transgenic mice from embryonic stem cells, as embryonic stem cells can easily be screened for a desired

integration event. When transgenic animals are produced by micro-injection, the transgene can integrate anywhere in the genome, resulting in the position effects and unpredictability referred to by the Examiner, but with gene trapping desired integrations (where the construct has integrated adjacent to an active promoter) can be detected and selected for. The selected cells can then be used to generate transgenic mice by injecting Embryonic Stem cells into blastocysts to obtain chimaeric mice. The distinction between the methods of Wall and the present invention is made clearer by the last paragraph of page 58 which indicates that Wall's constructs comprise genes with their own regulatory elements (often an enhancer and promoter) and are not gene trap vectors.

Houdebine is also concerned with a different technology to the present invention. As indicated by the title and abstract, this document concerns the production of pharmaceutical proteins from transgenic animals. The vectors described in Houdebine include regulatory regions, for example for directing expression in mammary glands (pages 272-273, section 4.1). The Examiner has referred to a passage on page 275, column 1, first paragraph which states that there are no general rules for obtaining good expression of transgenes. However, this passage is not concerned with gene trapping or random integration of constructs as claimed in the present invention but integration of constructs containing regulatory elements through micro-injection, a process in which the integration site is very critical for effective expression of the transgene. It is clear from page 277, column 1, paragraph 2 that Houdebine is concerned with the same methods of creating transgenic animals as Wall. Thus, passages such as page 279, column 2, final paragraph cannot be relevant to the present invention as they deal with a completely different technology.

As for the Examiner's objections to Claims 28 and 29, this objection should be withdrawn in light of the above arguments. The generation of transgenic mice from embryonic stem cells comprising the claimed construct would have been routine at the priority date (see for example the above quoted passages in Joyner and Gossler).

The Examiner's specific objections against Claims 22-24, 26-29 and 41 appear similar to the objection discussed above concerning unpredictability. Thus, please refer to the above arguments. Additionally, although random integration events may not always result in the integration of the heterologous gene in an appropriate position and orientation relative to an endogenous promoter such that the heterologous gene will be expressed, such rare integration events can be detected using the gene trap technology. Thus there is no need of excessive trial and error. Rather, the gene trap experiment can be carried out and successful integration events can be detected and selected for as indicated above.

Further, it is not necessary to know into which the construct has inserted in order to use the invention, as the heterologous gene in the construct will be expressed when the construct integrates under the control of any endogenous promoter. The endogenous gene can, of course, subsequently be identified, but this goes beyond the claimed method. Therefore, all claims are in condition for allowance under §112.

Claims 22-24, 26-29, 32-34 and 41-42 are in Condition for Allowance

Under 35 U.S.C. §102(e)

The Examiner rejected claims 22-24, 26, 28-29, and 32-33 under 35 U.S.C. §102(e) as being anticipated by Tessier-Lavigne et al. (U.S. Patent No. 6,248,934). The rejection should be withdrawn, based on the arguments above, all the claims are entitled to the priority date of April 21, 1993, and thus pre-date the Tessier-Lavigne patent.

Thus, for the reasons set forth, claims 22-24, 26-34, 41-42, and 47-74 are in condition for allowance.

Terminal Disclaimer to Parent Application

With respect to the Office Action of February 6, 2003, Applicants will file a terminal disclaimer to those claims having priority to U.S. Serial No. 08/537,765, filed April 21, 1994, now U.S. Patent No. 6,150,169; once a Notice of Allowance has been issued.

In view of the foregoing, it is respectfully submitted that the present application is now in proper condition for allowance. If the Examiner believes there are any further matters which need to be discussed in order to expedite the prosecution of the present application, the Examiner is invited to contact the undersigned.

If there are any fees necessitated by the foregoing communication, please charge such fees to our Deposit Account No. 50-0902, referencing our Docket No. (78870/32932).

Respectfully submitted,

TUCKER ELLIS & WEST LLP

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CERTIFICATE OF MAILING UNDER 37 C.F.R. §1.8

I hereby certify that this correspondence (along with any paper referenced as being attached or enclosed) is being deposited on the below date with the United States Postal Service with sufficient postage as first class mail in an envelope addressed to Commissioner for Patents, Mail Stop RCE, P.O. Box 1450, Alexandria, VA 22313-1450.

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